Remarks

Applicants have received and reviewed the Office Action dated June 3, 2010. Applicants request entry of this response and reconsideration of the rejection of the claims

By way of response, Applicants have cancelled claim 8 without prejudice. Applicants reserve the right to pursue the subject matter of this claim in a continuation application.

Claims 1, 9, 15, 17, and 31 have been amended. New claim 35 has been added. The amendments and new claims are supported throughout the specification including the originally filed claims. Support for this amendment may be found on at least page 13, line 20 of the PCT specification.

35 U.S.C. § 102(b)

Claims 1-3, 9, 11-22, 25, 28 and 29 were rejected under 35 U.S.C. § 102(b) as anticipated by Pouliquen, 2001. Claims 1-4, 9, 11-17, 19-22 and 25 were rejected under 35 U.S.C. 102(b) as anticipated by Widder et al., US 4,247,406. Claims 1-4, 9, 11-22 and 25 were rejected under 35 U.S.C. 102(e) as being anticipated by Chatterjee et al., US 2004/0065969. Applicants traverse these rejections.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); See also, MPEP §2131. Applicants submit that cited reference does not disclose all of the elements of the rejected claims.

Pouliquen (2001)

Applicants submit that the Pouliquen reference does not disclose a microparticle composition wherein the composition has a VAR of at least about 1 Watts/ cm^3 under alternating magnetic field conditions suitable for use in a patient and a density of about 2.7. Applicants reiterate the previously presented argument that parameters such as average particle size and size distribution are crucial; surface characteristics and interaction effects between neighboring particles all combine together to determine how much heat (i.e. the SAR, VAR or W/g) is produced under specified magnetic field conditions of frequency and strength. The Applicants have worked hard to produce the microparticle composition as presently claimed, in which all these parameters have been controlled to the point where useful levels of VAR or W/g are achieved. It can only be done by considering the whole microparticle construct, that is, the

nanomagnetic particles embedded in a polymer matrix, as a whole. Indeed, the Applicants are of the opinion that none of the micro-particles systems disclosed in the cited literature could achieve the levels of VAR as currently claimed and subject to the same magnetic field conditions because the micro-particles of the cited document were never designed for such a purpose. As such, it would be extremely unlikely for the micro-particles of the cited document to achieve useful VARs purely by accident.

For at least these reasons, the cited reference does not disclose all of the elements of the claims. Based on the foregoing, Applicants request withdrawal of the 102 (b) rejection of these claims.

Widder (US 4,247,406)

Applicants submit Widder neither teaches nor suggests a VAR or the density of the micro-particle composition as claimed.

Widder is concerned with the use of a magnetic field to concentrate therapeutics and diagnostics to an area to be treated. It is not concerned with the heating of an area to be treated using hysteresis effects. Therefore, there is no teaching or suggestion that the nanomagnetic particles must be distributed throughout the matrix to avoid aggregation. At column 3, lines 34-46, the document teaches away from a uniform distribution of magnetic particles in the matrix. Thus, it is clear the aim of the microspheres of Widder is to localize the therapeutic agent to an area to be treated and there is no concern as to the VAR generated by the microsphere or its capacity to heat a specific site. In addition, Widder teaches the use of a magnetic field to either draw or hold the microspheres towards or in the capillary bed (see column 3 lines 1-22). There is no teaching or suggestion that the magnetic particles are used to heat tissue.

Furthermore, at column 7, lines 7-22, Widder teaches that the magnetic field creates a magnetic induction of 8,000 gauss when an aqueous suspension of the microspheres is pumped at a particular rate through a conduit. The reason for the magnetic induction is to ensure at least 90% of the microspheres are immobilized in the area to be treated with a therapeutic agent. There is no teaching or suggestion that the magnetic particles embedded in the matrix are capable of achieving the VAR of the microspheres of the present invention when subjected to a magnetic field.

For at least these reasons, the cited reference does not disclose all of the elements of the claims. Based on the foregoing, Applicants request withdrawal of the 102 (b) rejection of these claims.

Chatterjee (US 2004/065969)

Applicants submit that the Chatterjee reference does not disclose a microparticle composition wherein the composition has a VAR of at least about 1 Watts/ cm^3 under alternating magnetic field conditions suitable for use in a patient and a density of about 2.7. The Chatterjee reference describes methods for microencapsulation of an agent where the agent could be magnetic nanoparticles of size 5 to 50 nm. Up to 40% of the weight of the microparticle could be the "agent" and the microparticle can be up to 1000 nm in size. These particles can be manipulated by magnetic fields, i.e. used for separation from a fluid medium. There is no teaching of using these particles for hyperthermia, no mention of specifically addressing any of the problems associated with trying to maximize heating, no discussion of measurements of SAR or VAR and no mention of the need to disperse the particles throughout the matrix to avoid aggregation. Thus, the cited reference does not disclose all of the elements of the claims.

For at least these reasons, the cited reference does not disclose all of the elements of the claims. Based on the foregoing, Applicants request withdrawal of the 102 (b) rejection of these claims.

35 U.S.C. § 103(a)

Claims 1-4, 8-22, 25 and 28-31 were rejected under 35 U.S.C. § 103(a) over Gray et al., US 6,167,313 in view of Lesniak et al., US 6,541,039 and Handy et al, US 6,997,863. Claim 8 has been cancelled rendering the rejection of this claim moot. Applicants traverse this rejection.

The recent Supreme Court case, *KSR Int 'I Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007), sets forth the legal standard for obviousness. This case reaffirms the analytical framework set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), which mandates that an objective obviousness analysis includes: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; and (3) resolving the level of ordinary skill in the pertinent art. Id. at 1734. Secondary considerations such as commercial success, long felt but unsolved needs, or failure of others may also be persuasive.

In rejecting claims under 35 U.S.C. § 103(a), the Examiner bears the initial burden of establishing a prima facie case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Only if this initial burden is met does the burden of coming forward with evidence or argument shift to the appellant. *Id.* at 1445. Obviousness is then determined on the basis of the evidence as a whole and the relative persuasiveness of the arguments. *See Oetiker*, 977 F.2d at 1445. One criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that claimed subject matter should be carried out and would have a reasonable likelihood of success viewed in light of the prior art. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

"It remains important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007). "Hindsight" is inferred when the specific understanding or principal within the knowledge of one of ordinary skill in the art leading to the modification of the prior art in order to arrive at appellant's claimed invention has not been explained. *In re Rouffet*, 149 F.3d 1350, 1358 (Fed. Cir. 1998). The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). The claimed subject matter is nonobvious if it involves a number of complex and unpredictable alternatives and there is no reason one of skill in the art would select one alternative over another. *Ortho-McNeil vs. Mylan, Inc*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Applicants' claims including claim 1 now specify that the microparticle composition has a density of about 2.7 or less and a VAR of at least about 1 Watts/cm^3. the cited references in combination do not disclose all of the elements of the claims and there would be no reason to modify the primary reference.

The Examiner concedes that Gray does not teach the magnetic material in the form of nanoparticles. As discussed above, the use of nanoparticles is different than other types of particles. Gray does not suggest the required VAR to heat a sample in specified magnetic field conditions. The Examiner has argued that the method described in Example 1 of Gray to produce microspheres is similar to the method of the present invention. The methods of Gray are different than those of the instant application. More specifically, the inventors of the present invention

found that the aggregation of nanomagnetic particles was an important point when obtaining the correct VAR. The method of Gray at Column 12, lines 29-51 teaches a mixture of magnetic particles and Biopol in dichloromethane. This mixture was then dropped into a solution of poly-vinyl alcohol and mixed with homogenization. The mixture was allowed to mix for 60 minutes to allow all the dichloromethane to evaporate.

In contrast, the method of the present invention requires the mixture of nanomagnetic particles and matrix to undergo sonication, specifically to ensure the disbursement of the nanomagnetic particles throughout the matrix. This step is neither taught nor suggested by Gray. In fact, the mixture is only mixed to allow for the dichloromethane to evaporate and does not mention sonication. A person skilled in the art would be aware of various differences between homogenization, sonication and mixing by stirring, and that these are not the same techniques.

Furthermore, in Example 1, Gray teaches the heating efficiency analysis involved measuring the hysteresis loop of each material (see Column 12, lines 13-18). In contrast, the present invention is not concerned with the hysteresis loop. We refer the Examiner to page 10, lines 15-20 of the specification as originally filed, where it teaches the magnetic particles do not heat via the hysteresis loop. Therefore, the microparticles of Gray are not the same as the present invention.

The deficiencies of Gray are not remedied by reference to Handy or Lesniak. Although the particles of Lesniak may be subjected to an alternating magnetic field to heat the iron core, Lesniak does not teach or suggest the SAR, VAR or preferred magnetic field conditions claimed in the amended claims. Similarly, Lesniak does not provide any information regarding the density of the coated particles or the fractional loading of magnetic oxide within the particles. Further, the size range of the microparticles of the present invention is substantially different from that disclosed in Lesniak. Handy is directed towards a method based on the administration of a plurality of single domain nanomagnetic particles attached to a ligand. However, the document neither teaches nor suggests the distribution of the nanomagnetic particles within a matrix, the required VAR or SAR or the size or specific heating conditions. Thus, the secondary references in combination with Gray do not disclose all of the elements of the claims.

There would be no reason to combine the particles of Lesniak or Handy with the composition of Gray. Both Lesniak and Handy are directed to administration of single nanoparticles that are small enough to penetrate the tissue. The ability of these smaller particles

to penetrate the tissue or be targeted to the tissue is essential to the function of the particles to provide sufficient heating. According to Lesniak larger particles in the micron range would not be able to penetrate the tissue and would not be retained in the tissue due to diffusion and tumor pressure. See col. 6, lines 33-46. With regard to Handy, encapsulating the nanoparticle in a matrix would prevent the targeting to tissue through the use of an antibody. Incorporating the nanoparticle of Handy into the matrix of Gray would render the composition of handy inoperable for cell type targeting. Thus, there would be no reason to combine the teachings of the references as both secondary references are directed to targeting individual nanoparticles to tissues.

Based on the foregoing, Applicants request withdrawal of the rejection.

Claims 1-4, 8-22, 25 and 28-31 were rejected under 35 U.S.C. 103(a) over Jones et al., 2001. Applicants traverse the rejection.

The journal article by Jones et al., (2001) describes the use of microspheres formulated to contain non-superparamagnetic ferromagnetic particles, which are much larger than the nanomagnets used in the microparticles claimed in the present application. In fact, this article serves to highlight the exact problem the inventors had to overcome by using nanomagnets. That is, when the field strength used in the experiments described is 40 kA/m (approx 500 Oe - see p 389) it is far greater than the 60 to 120 Oe claimed in the present application which is clinically acceptable. The ferromagnetic particles used in the reported experiments in rabbit kidneys would not produce useful heating at the clinically acceptable magnetic field levels. Thus Jones et al., (2001) highlights the problems associated with using targeted heating but does not provide any solution to the problem. Thus, Jones, does not disclose a microparticle composition comprising nanomagnetic particles and a matrix, wherein the composition has a density of about 2.7 or less and a VAR of at least about 1 Watts/cm^3.

Although the particles of Lesniak may be subjected to an alternating magnetic field to heat the iron core, Lesniak does not teach or suggest the SAR, VAR or preferred magnetic field conditions claimed in the amended claims. Similarly, Lesniak does not provide any information regarding the density of the coated particles or the fractional loading of magnetic oxide within the particles. Further, the size range of the microparticles of the present invention is substantially different from that disclosed in Lesniak. Handy is directed towards a method based on the administration of a plurality of single domain nanomagnetic particles attached to a ligand. However, the document neither teaches nor suggests the distribution of the nanomagnetic

particles within a matrix, the required VAR or SAR or the size or specific heating conditions. Thus, the secondary references in combination with Jones do not disclose all of the elements of the claims.

There would be no reason to combine the particles of Lesniak or Handy with the composition of Jones. Both Lesniak and Handy are directed to administration of single nanoparticles in a fluid that are small enough to penetrate the tissue. The ability of these smaller particles to penetrate the tissue or be targeted to the tissue is essential to the function of the particles to provide sufficient heating. According to Lesniak larger particles in the micron range would not be able to penetrate the tissue and would not be retained in the tissue due to diffusion and tumor pressure. See col. 6, lines 33-46. With regard to Handy, encapsulating the nanoparticle in a matrix would prevent the targeting to tissue through the use of an antibody. Incorporating the nanoparticle of Handy into the matrix of Jones would render the composition of handy inoperable for cell type targeting. Thus, there would be no reason to combine the teachings of the references as both secondary references are directed to targeting individual nanoparticles to tissues.

35 U.S.C. § 112

Claim 9 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. While not acquiescing to the rejection and solely to expedite prosecution, Applicants has amended claim 9 to refer to particle sizes of about 10 to 50 microns. Applicants request withdrawal of the rejection.

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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